

This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

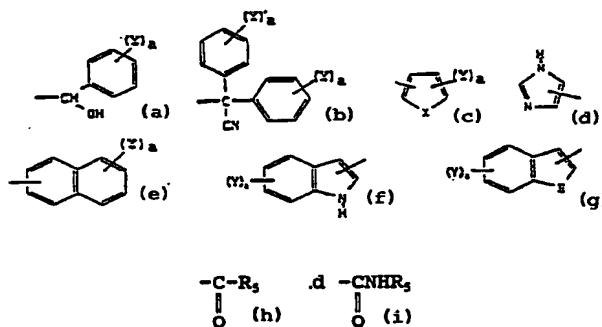
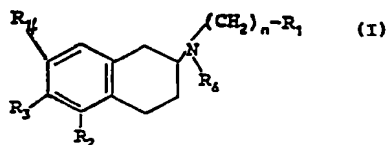
**As rescanning documents *will not* correct images,
please do not report the images to the
Image Problem Mailbox.**



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 31/44, 31/415, 31/405 A61K 31/38, 31/385, 31/34 A61K 31/275, 31/135	A1	(11) International Publication Number: WO 90/13294 (43) International Publication Date: 15 November 1990 (15.11.90)
(21) International Application Number: PCT/US90/02135 (22) International Filing Date: 19 April 1990 (19.04.90) (30) Priority data: 349,091 9 May 1989 (09.05.89) US (71) Applicant: WHITBY RESEARCH, INC. [US/US]; 1001 Health Sciences Road West, Irvine, CA 92715 (US). (72) Inventor: BELLUZZI, James, D. ; 4881 Rain Tree Lane, Irvine, CA 92715 (US). (74) Agent: HACKLER, Walter, A.; 2372 S.E. Bristol, Suite B, Santa Ana Heights, CA 92707 (US).		(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>

(54) Title: A METHOD OF REDUCING BODY WEIGHT AND FOOD INTAKE USING A DOPAMINE D2 RECEPTOR AGONIST

**(57) Abstract**

This invention provides a method for treating the symptoms of obesity which comprises administering to a human or other mammal suffering from the symptoms of obesity an effective amount of a compound selected from the group consisting of the optically active compounds especially the (-) negative stereoisomers represented by formula (I), wherein R_1 is selected from the group consisting of methyl, substituted or unsubstituted phenyls, pyridyl, hydroxyphenyl, (a), (b) (c), (d), (e), (f), (g), X is oxygen or sulfur, Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxyamido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and hetero atom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorus and said hydrocarbyl radicals comprise from 1 to 12 carbon atoms, and a is an integer of from zero to 3, R_2 , R_3 and R_4 are each selected from the group consisting of H and OA, A is H or is selected from the group consisting of hydrocarbyl radicals, (h) and (i), R_5 is selected from the group consisting of hydrocarbyl radicals; n is an integer between 1 and 3; and R_6 is an alkyl chain having between 1 and 3 carbon atoms with the provision that at least one of R_2 , R_3 and R_4 is H, that at least one of R_2 , R_3 and R_4 is not H, and that R_2 and R_4 are not both OA, and pharmaceutically acceptable salts thereof. Preferably, R_2 is oxygen. Most preferably, R_2 is OA and A is H, and the compound is the (-) isomer.

DESIGNATIONS OF "DE"

Until further notice, any designation of "DE" in any international application whose international filing date is prior to October 3, 1990, shall have effect in the territory of the Federal Republic of Germany with the exception of the territory of the former German Democratic Republic.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MC	Monaco
AU	Australia	FI	Finland	MG	Madagascar
BB	Barbados	FR	France	ML	Mali
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GR	Greece	NL	Netherlands
BJ	Benin	HU	Hungary	NO	Norway
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	SD	Sudan
CF	Central African Republic	KP	Democratic People's Republic of Korea	SE	Sweden
CG	Congo	KR	Republic of Korea	SN	Senegal
CH	Switzerland	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
DE	Germany, Federal Republic of	LU	Luxembourg	TG	Togo
DK	Denmark			US	United States of America

-1-

A METHOD OF REDUCING BODY WEIGHT AND FOOD INTAKE
USING A DOPAMINE D2 RECEPTOR AGONIST

Field of Invention

This invention relates to compositions comprising a dopaminergic agent and to a method for administering said compositions in an amount effective to induce anorexia and weight loss in the body of a human or animal.

Introduction

The search for drugs useful as diet aids is ongoing. The amphetamines have been enlisted for the purpose of inducing weight loss, but their undesirable side effects include restlessness, irritability, and panic, among others. Moreover, it has been found that weight loss induced by amphetamines in obese humans is due almost entirely to reduced food intake, rather than to increased metabolism, and tolerance to accepted doses develops rapidly. (Goodman, L.S., The Pharmacological Basis of Therapeutics, 7th Ed., MacMillan, New York, 1985, pp. 166-67).

Dopamine systems in the central nervous system have long been implicated in the anorexic effects of stimulant drugs such as amphetamine. Direct tests of dopaminergic involvement have become possible with the discovery of more specific dopamine agonists. Anorexia was produced in rats given dopamine agonists such as lisuride, lergotrile and bromocriptine (Carruba, M.O., Ricciardi, S., Muller, E. E. and Mantegassa, P., "Anorectic effect of lisuride and other ergot derivatives in the rat," Eur. J. Pharmacol. 64:133-141, 1980.) More recently a related dopamine agonist, pergolide was shown to induce anorexia in rodents, but repeated administration produced tolerance to the anorexic effects (Greene, S. B., Mathews, D., Hollingsworth, E. M. and Garbin, C. P.,

SUBSTITUTE SHEET

-2-

"Behavioral effects of pergolide mesylate on food intake and body weight," Pharmac. Biochem. Behav. 23:161-167, 1985.)

The role of specific dopamine receptor subtypes in the anorexic actions of dopamine agonists has been studied recently. For instance, amphetamine-induced anorexia was blocked by the selective dopamine D1 receptor antagonist SCH 23390, but not by the selective D2 receptor antagonist sulpiride. This discovery suggests that amphetamine produces anorexia by stimulation of the dopamine D1 receptor (Gilbert, D. B. and Cooper, S. J., "Analysis of dopamine D1 and D2 receptor involvement in d- and l-amphetamine-induced anorexia in rats," Brain Res. Bull. 15:385-389, 1985.) However, Rusk, I. and Cooper, S. J. ("Dopamine D1 and D2 receptors in relation to palatable food consumption in the rat," Soc. Neurosci. Abst. 12:1557, 1986) reported anorexic effects following administration of selective dopamine D2 receptor agonists RU24213 and N-0437. Furthermore, it has been found that the anorexic effects of N-0437 are completely antagonized by the selective D2 antagonist, YM-09151-2 (Rusk, I. N. and Cooper, S. J., "Profile of the selective dopamine D-2 receptor agonist N-0437: its effect on palatability- and deprivation-induced feeding, and operant responding for food," Physiol. Behav. 44:545-553, 1988.) In support of the hypothesis that D2 receptors play a role in anorexia, it was recently reported that sulpiride, a D2 receptor antagonist, but not SCH 23390, a D1 receptor antagonist, blocks anorexia produced by apomorphine (Towell, A., Willner, P., and Muscat, R., "Apomorphine anorexia: the role of dopamine receptors in the ventral forebrain," Psychopharmacology 96:135-141, 1988.)

However, the ability of compounds known to produce temporary loss of appetite in an animal to which it is administered does not necessarily predict that sustained weight loss can be achieved in animals or humans to which the same drug is administered over a period of weeks. The temporary anorexia induced in an animal during a 30-minute

SUBSTITUTE SHEET

-3-

feeding test, for instance, does not predict whether the animal will experience a rebound effect as soon as the drug wears off such that food consumption over a 24-hour period is the same with or without administration of the drug despite a brief period of drug-induced reduced food intake.

In addition, although it is known that for many dopamine D2 agonists one stereoisomer will generally have considerably greater potency in reducing food intake, no studies have been conducted to determine which isomer induces the greatest weight loss.

The need exists for more and better drugs useful in the treatment of obesity in humans and other animals. Especially, the need exists for drugs that cause a minimum of undesirable side effects at therapeutic dosages and for drugs that do not show tolerance in the subject upon prolonged administration, but are capable of inducing sustained weight loss without a rebound effect upon their withdrawal.

A Brief Description of the Figures of the Drawing

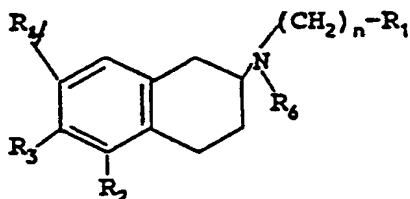
Figure 1 of the drawing is a graph showing the effects of dopamine agonists on body weight. Figure 2 of the drawing is a graph showing the effect of continuous 24-hour infusion of N-0923 on body weight in free-feeding rats. Figure 3 of the drawing is a graph showing the influence of starting body weight on the anorexic effects of N-0923. Figure 4 is a graph comparing affects of 1 week and 4 weeks of continuous infusions of N-0923.

Summary of the Invention

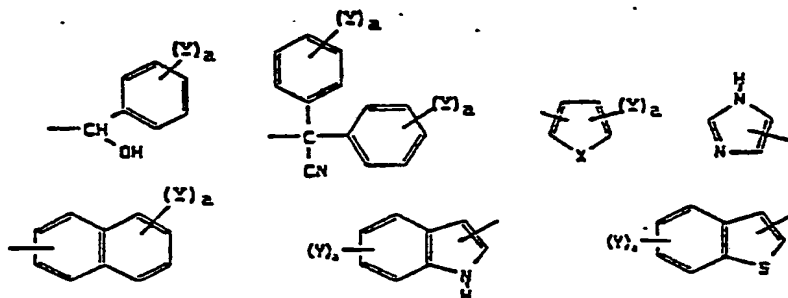
This invention provides a method for inducing anorexia and weight loss in mammals, e.g., humans, which comprises administering to a mammal suffering from obesity an effective amount of a compound selected from the group of optically active compounds represented by the general formula:

SUBSTITUTE SHEET

-4-



wherein R_1 is selected from the group consisting of methyl, substituted or unsubstituted phenyls, pyridyl, hydroxyphenyl,



X is oxygen or sulfur, Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxyamido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and hetero atom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorus and said hydrocarbyl radicals comprise from 1 to 12 carbon atoms, and a is an integer of from zero to 3,

R_2 , R_3 and R_4 are each selected from the group consisting of H and OA, A is H or is selected from the group consisting of hydrocarbyl radicals, $-C-R_5$, and $-CNHR_5$,



R_5 is selected from the group consisting of hydrocarbyl radicals; n is an integer between 1 and 3; and R_6 is an alkyl chain having between 1 and 3 carbon atoms with the provision that at least one of R_2 , R_3 and R_4 is H, that at least one of R_2 , R_3 and R_4 is not H, and that R_2 and R_4 are not both OA,

SUBSTITUTE SHEET

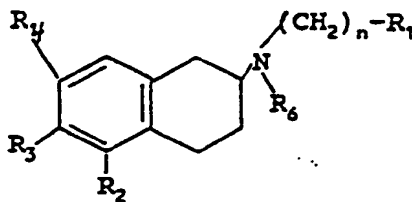
-5-

except that when R_1 is meta-hydroxyphenyl, phenyl, or 2-thienyl, the compound is optically active and pharmaceutically acceptable salts thereof. Preferably, R_2 is oxygen.

It is essential that the compound selected for use in the method of the present invention be an optically active compound or mixture thereof capable of selectively activating either the postsynaptic or the presynaptic D2 dopamine receptor, e.g., in a human. In particular, it is found that the (+) and (-) enantiomers of 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethylamino)tetralin are especially preferred for use in the methods of inducing anorexia and weight loss of the present invention.

Detailed Description of the Invention

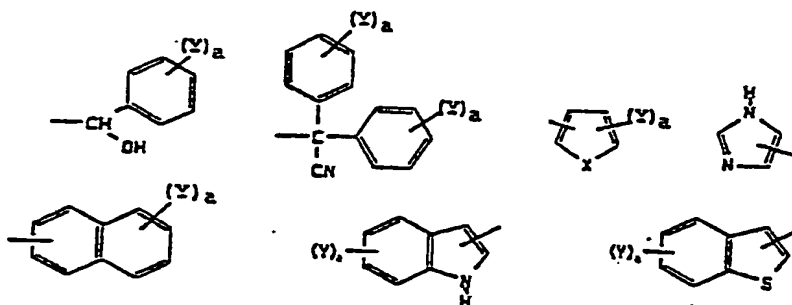
The compounds used in the present invention are selected from the group of stereoisomers or mixtures thereof of compounds represented by the general formula:



wherein R_1 is selected from the group consisting of organic radicals methyl, substituted or unsubstituted phenyls, pyridyl, hydroxyphenyl,

SUBSTITUTE SHEET

-6-



X is oxygen or sulfur, Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxyamido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and hetero atom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorus and said hydrocarbyl radicals comprise from 1 to 12 carbon atoms, and a is an integer of from 0 to 3,

R_2 , R_3 and R_4 are each selected from the group consisting of H and OA, A is H or is selected from the group consisting of hydrocarbyl radicals, $-C-R_5$, and $-CNHR_5$,



R_5 is selected from the group consisting of hydrocarbyl radicals; n is an integer between 1 and 3; and R_6 is an alkyl chain having between 1 and 3 carbon atoms with the provision that at least one of R_2 , R_3 and R_4 is H, that at least one of R_2 , R_3 and R_4 is not H, and that R_2 and R_4 are not both OA, except that when R_1 is meta-hydroxyphenyl, phenyl, or 2-thienyl, the compound is optically active and pharmaceutically acceptable salts thereof. Preferably, R_2 is oxygen.

A is preferably H or is selected from the group consisting of phenyl and alkyl radicals having from 1 to 12 carbon atoms, and more preferably R^5 is an alkyl or aryl radical that would

SUBSTITUTE SHEET

-7-

serve to extend the activity of the compound in the body, for example phenyl, methyl t-butyl, d-methylphenyl, o-, m- or p-methoxyphenyl, or nonyl.

The more preferred groups represented by R_1 are thienyl, phenyl, hydroxyphenyl, furanyl and naphthalenyl, e.g., 2-thienyl, 3-thienyl, 3-hydroxyphenyl, 4-hydroxyphenyl, etc.

In the more preferred compounds for use in the present invention n is 2 and R_2 is OA; and most preferably A is H and R_3 is propyl.

In one embodiment of the invention, the compound selected for use in the method of inducing anorexia and weight loss is an optically active compound or mixture thereof capable of substantially activating the postsynaptic dopamine D2 receptor, e.g., in a human. It has been found that the negative isomers of the claimed compounds possess the ability to predominately stimulate postsynaptic D2 dopamine receptors. As is shown in the Examples hereafter, the (-) isomers are unexpectedly more potent than the positive isomers for inducing anorexia and long term weight loss. A loss of as much as 12 percent of body weight has been achieved by administering a (-) isomer. However, at high dosages, for example, 3 mg/kg, the (-) isomers have been found to induce undesirable side effects of the central nervous system, such as stereotypy in rats.

In particular it has been found that the (-) isomer of 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethylamino)tetralin is especially preferred for use in the method of the present invention because the (-) isomer is a strong agonist at postsynaptic receptors and possesses unexpectedly high potency for inducing anorexia and weight loss. U.S. patent application

INSTITUTE SHEET

-8-

Serial No. 206,193 filed June 13, 1988, entitled "Method and Compositions for Treatment of Parkinsonism Syndrome in Mammals," which is hereby incorporated by reference in its entirety, discloses tests showing the preferential stimulation of post-synaptic dopamine D2 receptors by the (-) isomer of compounds used in the present invention.

In another embodiment of the invention, the positive (+) isomers of the compounds disclosed herein are preferred in the method of inducing anorexia and weight loss because at therapeutic doses the (+) isomers produce fewer side effects showing undesirable central nervous system involvement, such as stereotypy in rats. This freedom from side effects persists at dosages ten times as high as the effective dose for the (-) isomer. The (+) isomers of the compounds of the invention are known to be more efficacious at presynaptic than at postsynaptic D2 dopamine receptors and while not wishing to be bound by theory, it is believed that the (+) isomers produce no side effects at the dosages preferred herein because they act preferentially at presynaptic D2 dopamine receptor sites or at a different subset of postsynaptic receptors than do the (-) isomers. It should be remembered, however, that the (+) isomers require a dosage much higher than that required to achieve comparable weight loss using the (-) isomer, i.e., more than ten times as much (+) isomer is required as is needed for comparable result if the (-) isomer is employed.

Thus, the embodiment of the invention employing the (+) isomer should be practiced when it is practical to administer a higher effective dosage of dopaminergic compound to achieve the advantage of avoiding the risk of side effects to the central nervous system. It is preferred that the (+) isomer of 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethylamino)tetralin

SUBSTITUTE SHEET

-9-

be employed to achieve anorexia and weight loss without danger of producing side effects at high dosage.

The above compounds may be made by any of the methods disclosed in U.S. Patent 4,564,628 entitled "Substituted 2-Aminotetralins," which is hereby incorporated by reference. A method for resolving the compounds into (+) and (-) isomers is disclosed in Example 1 hereinafter.

For purposes of this invention, designation of the (-) isomer shall mean that the (-) isomer is present in excess of the (+) isomer. Preferably, the mixture is greater than 90 mole percent of the (-) isomer. Most preferably, the (-) isomer is substantially pure, i.e., greater than 99 mole percent. Designation of the (+) isomer is defined by inverse analogy, i.e., most preferably the (+) isomer is substantially pure., i.e, greater than 99 mole percent.

In one group of compounds, R₁ is selected from the group consisting of radicals represented by the general formula:



wherein X is oxygen or sulfur. Specific preferred compounds of this group include:

2-(N-n-propyl-N-2-[2-thienyl]ethylamino)-5-hydroxy-tetralin,

2-(N-n-propyl-N-2-[3-thienyl]ethylamino)-5-hydroxy-tetralin,

2-(N-n-propyl-N-2-[2-furanyl]ethylamino)-5-hydroxy-tetralin,

2-(N-n-propyl-N-2-[3-furanyl]ethylamino)-5-hydroxy-tetralin,

SUBSTITUTE SHEET

-10-

2-(N-n-propyl-N-2-[2-thienyl-4-methyl]ethylamino)-5-hydroxytetralin,

2-(N-n-propyl-N-2-[2-thienyl-3,4,5-trimethyl]ethylamino)-5-hydroxytetralin,

2-(N-n-propyl-N-2-[2-thienyl-5-chloro]ethylamino)-5-hydroxytetralin,

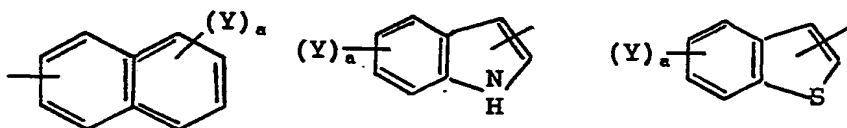
2-(N-n-propyl-N-2-[2-(4-bromo-5-methyl)thienyl]ethylamino)-5-hydroxytetralin,

2-(N-n-propyl-N-2-[2-(4-methyl-5-ethyl)thienyl]ethylamino)-5-hydroxytetralin,

2-(N-n-propyl-N-2-[2-benzothienyl]ethylamino)-5-hydroxytetralin and

2-(N-n-propyl-N-2-[3-benzothienyl]ethylamino)-5-hydroxytetralin.

In a second group of compounds, R_1 is selected from the group of radicals represented by the general formulae:



wherein Y and a are as defined above. More preferably, Y comprises no more than 5 carbon atoms and a is 0 or 1. Specific preferred compounds of this group include:

2-(N-n-propyl-N-2-[2-naphthalenyl]ethylamino)-5-hydroxytetralin,

2-(N-n-propyl-N-2-[4-indolyl]ethylamino)-5-hydroxytetralin,

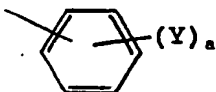
2-(N-n-propyl-N-2-[2-benzothienyl]ethylamino)-5-hydroxytetralin, and

2-(N-n-propyl-N-2-[3-benzothienyl]ethylamino)-5-hydroxytetralin;

SUBSTITUTE SHEET

-11-

In yet another group of compounds, R^1 is phenyl and/or substituted phenyl and is selected from the group of radicals represented by the general formula:



wherein Y and a are as defined above. Specific preferred compounds of this group include:

2-(N-n-propyl-N-2-[phenyl]ethylamino)-5-hydroxy-tetralin,

2-(N-n-propyl-N-2-[4-hydroxyphenyl]ethylamino)-5-hydroxytetralin, and

2-(N-n-propyl-N-2-[3-hydroxyphenyl]ethylamino)-5-hydroxytetralin;

This invention provides a method of treatment of the symptoms of obesity by inducing anorexia and weight loss, which method comprises administering a therapeutically effective amount of one of the foregoing compounds to a patient suffering such symptoms. Even more preferably, the method of the present invention comprises administering the (-) isomer of 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethyl-amino)tetralin to a human or other mammal to reduce the symptoms of obesity.

The pharmaceutically effective dose will generally be selected within the above range so as to avoid undesirable side effects to the central nervous system while achieving significant antiobesity effects.

In general, a pharmacologically-effective daily dose can be from 0.01 mg./kg. to 100 mg./kg. per day, bearing in mind, of course, that in selecting the appropriate dosage, in any specific case, consideration must be given to the patient's

SUBSTITUTE SHEET

-12-

weight, general health, metabolism, age and other factors which influence response to the drug. A preferred dosage is 0.3 to 3 mg./1 kg. of body weight. A particularly preferred dose is 0.3 mg./kg. per day.

The pharmaceutical composition may be in a form suitable for oral use, for example, as tablets, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients can be, for example, inert diluents, for example calcium carbonate, sodium carbonate, lactose, calcium phosphate, or sodium phosphate; granulating and disintegrating agents, for example maize starch, or alginic acid; binding agents, for example starch, gelatine, or acacia; and lubricating agents, for example magnesium stearate, stearic acids, or talc. The tablets can be uncoated or they can be coated by known techniques to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

Formulations for oral use may also be presented as hard gelatine capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate, or kaolin, or as soft gelatine capsules wherein the active ingredient is mixed with an oil medium, for example archis oil, liquid paraffin, or olive oil.

SUBSTITUTE SHEET

-13-

Aqueous suspensions contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth, and gum acacia; dispersing or wetting agents may be naturally-occurring phosphatides, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecethylenoxy-cetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example, polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, n-propyl, or p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents may also be present.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, preservative,

SUBSTITUTE SHEET

-14-

flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example as sterile injectable aqueous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butane diol.

The pharmaceutical compositions may be tableted or otherwise formulated so that for every 100 parts by weight of the composition there are present between 5 and 95 parts by weight of the active ingredient. The dosage unit form will generally contain between about 1 mg. and about 100 mg. of the active ingredient of the formula stated above.

From the foregoing discussion of formulations it is apparent that the compositions of this invention can be administered orally or parenterally. The term parenteral as used herein includes subcutaneous injection, intravenous, intramuscular, or intrasternal injection or infusion techniques, as illustrated in the following examples. The compositions can also be administered transdermally by topical administration to skin and mucosal membranes.

To illustrate the manner in which the invention may be carried out, the following examples are given. It is understood, however, that the examples are for the purpose of illustration and the invention is not to be regarded as limited to any of the specific materials or conditions therein.

SUBSTITUTE SHEET

-15-

Example 1

Racemic 2-(N-n-propylamino)-5-methoxytetralin was resolved into its (-) and (+) isomers according to the method of Ten Hoeve and Wynberg (J. Org. Chem. 1985, 50, 4508), using the (+) isomer of 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide.

6.23 gm. (28.5 mmol) of racemic 2-(N-n-propylamino)-5-methoxytetralin and 7.7 gm. (27.8 mmol) of (+) 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide were dissolved by warming in 33 ml. of absolute alcohol and 10 ml. of water. The heating was discontinued and the solution was allowed to cool while being stirred. After 15 min., the mixture was filtered off and washed with ether to yield 6.08 gm. of the salt (12.27 mmol, 43%). The salt was then stirred 30 min. with a solution of sodium hydroxide dissolved in 75 ml. water to which was added 25 ml. chloroform. After mixing, this was extracted with 2 x 50 ml. portions of chloroform. The organic extracts were washed with water, dried over magnesium sulfate and evaporated to dryness to yield 2.66 gm. (99%) of a slightly colored oil. The optical rotation for 49 mg. in 5 ml. of methanol was -62.4° (578 nm). (The (+) isomer can be similarly isolated by using (-) 4-(2-chlorophenyl)-5,5-dimethyl-2-hydroxy-1,3,2-dioxaphosphorinane 2-oxide.)

The resultant isomers of 2-(N-n-propylamino)-5-methoxytetralin are then converted to (+) and (-) 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethylamino)tetralin by the methods described in U.S. Patent No. 5,564,628 herein incorporated by reference.

SUBSTITUTE SHEET

-16-

Example 2

Male albino Sprague Dawley rats obtained from Charles River Labs, Wilmington, MA 01887 were used for all in vivo experiments. The animals were placed on a light/dark cycle with lights on from 7:00 a.m. to 7:00 p.m. and water and rat chow were made available ad lib unless otherwise noted. It should be noted that under ad lib conditions these caged animals normally undergo continuous weight gain throughout their adult lives subject only to the limitations of cage size. Therefore, in the following experiments weight loss must be judged against the continuous trend of weight gain the animal would have undergone, as is illustrated in each case by the weight of the vehicle control group.

The effects of the pure stereoisomers of 5-hydroxy-2-(N-n-propyl-N-2-[2-thienyl]ethylamine)tetralin, N-0923 (-) and N-9024 (+), upon food intake and weight gain of the rats were compared with those caused by d-amphetamine sulfate and apomorphine HCl (purchased from Sigma Chemical Co., St. Louis, MO.)

Animals were maintained in their home cages throughout the experiments and body weight and food intake were measured daily. Animals were weighed to the nearest 0.1 gm using an Ohaus animal balance. Food intake was determined by weighing the food pellets before the feeding session and subtracting the weight of the remaining food pellets plus spillage after the two-hour session using a Sartorius electronic balance. Drug treatments varied according to the particular experimental procedure as follows:

SUBSTITUTE SHEET

-17-

Experiment 1

Intraperitoneal injections on restricted feeding schedule

24 animals were put on a feeding schedule restricting access to normal lab chow to two hours each day between 14:00 and 16:00 hours. When all animals acclimated to the restricted schedule and food intake and weight gain stabilized, an injection was administered to each animal 30 minutes prior to the daily two hour feeding period. The animals received intraperitoneal injections of one of the following drugs prepared daily: as shown in Figure 1 N-0923 (0.3 (\diamond), 1 or 3 (\triangle) mg/kg), N-0924 (3 mg/kg (\square)), d-amphetamine (χ) (3 mg/kg), apomorphine (3 mg/kg) or distilled water vehicle (\blacklozenge) (1 ml/kg). An individual timer was used for each animal to insure that feeding commenced 30 minutes after the injections and that food was available for two hours. Each animal received 5 consecutive daily injections of one drug at a constant dose. Weight loss for each drug is shown in the difference in weights of the animals administered vehicle control and those of the animals administered the selected drug.

The data summarized in Table 1 show significant reduction of body weight at all doses of N-0923 tested (0.3-3 mg/kg). Fig. 1 shows the same data graphically. Body weight decreased rapidly during the first several days of treatment with N-0923, but then the effects appeared to tolerate and the animals' weight stabilized at a lower level. This new weight was maintained for the remainder of the 5-day test period, suggesting that the drug-treated animals were not gaining in a normal manner shown in the vehicle control group weight. Thus, while the anorexic effects appear to tolerate with 3-4 days, the animals did not display any rebound increase in feeding.

SUBSTITUTE SHEET

-18-

The animals receiving the highest dose of N-0923 (3 mg/kg) displayed stereotypic behavior, which might account for the reduced feeding. But it should be noted that the lowest dose of N-0923 (0.3 mg/kg) showed significant weight loss without any measurable stereotypic behavior. The animals receiving a comparable dose of amphetamine also exhibited side effects to the central nervous system including heightened excitability and some symptoms of stereotypy. No stereotypic behavior or other signs of increased nervousness or irritability were noticed in any animals receiving the (+) isomer.

Table 1
The effects of dopamine agonists
on body weight and food intake

<u>Drug</u>	<u>Dose</u> <u>(mg/kg)</u>	<u>N</u>	<u>Cumulative Change on Day Five(gm)</u>	
			<u>Body Weight</u>	<u>Food Intake</u>
Vehicle	-	5	12.9 ± 0.8	-0.1 ± 1.5
N-0923	0.3	3	-2.4 ± 2.9 ⁺	-5.9 ± 0.8*
N-0923	1.0	3	-6.3 ± 1.8 ⁺⁺	-2.3 ± 2.0
N-0923	3.0	3	-36.9 ± 4.3 ⁺⁺	-7.6 ± 2.1*
N-0924	3.0	3	8.7 ± 3.2	1.2 ± 1.7
Apomorphine	3.0	3	1.2 ± 5.0*	-0.2 ± 2.3
Amphetamine	3.0	3	-25.4 ± 1.9*	-6.2 ± 3.1*

*significantly different from vehicle $p < 0.05$;

⁺ $p < 0.01$;

⁺⁺ $p < 0.001$

The (-) isomer was slightly more potent than d-amphetamine in producing weight loss, although both produced significant weight loss (Table 1). While considerably less potent than the (-) isomer, N-0924, the (+) isomer, showed a slight trend to produce weight loss. Stereoselectivity of the antiobesity effect of N-0437 is, thus, illustrated by the substantial

SUBSTITUTE SHEET

-19-

increase in potency of the (-) isomer over the (+) isomer.

Experiment 2

Continuous 1-week drug infusion on free-feeding schedule

Body weight and food intake were recorded daily for 30 animals maintained on ad lib food and water. When weight and intake measurements had stabilized the animals were divided into treatment groups balanced to achieve equal mean body weights in each group (N=5/group). In the first phase, animals were implanted with Alzet osmotic minipumps (model 2ML1) designed to deliver 10 μ l/hour for 1 week.

Animals were lightly anesthetized with methoxyflurane and a small incision was made on the back of the animal at the level of the shoulders and the pumps were inserted () with the injection outlet pointed inward. As shown in Figure 2, three groups of 5 animals received either N-0923 (50 () or 200 () μ g/10 μ l) or vehicle (5% dextrose in water () at equal rates). In the second phase, 3 additional groups of 5 rats had their food intake restricted to produce weight loss to a starting weight equal to that induced by N-0923 (200 μ g/10 μ l/hr) in the previous experiment. After 3 days on this feeding schedule, 5 animals received minipump implants containing (N-0923 (200 μ g/10 μ l/hr). To test the effect of starvation in the above animals, 10 animals representing an unstarved control were allowed to free-feed for 24 hours, at which time they received minipump implants containing either N-0923 (200 μ g/ μ l/hr) or vehicle. All pumps were removed after one week and body weight and food intake measurements were taken for an additional week.

SUBSTITUTE SHEET

-20-

As is shown in the results summarized in Figure 2, continuous 24-hour infusion of N-0923 (Δ) and (\square) reduced body weight in free-feeding animals at both doses tested. But once again the anorexic effects tolerated after 3-4 days. This shows that the hunger produced by 22-hour food deprivation in Experiment 1 was not responsible for the tolerance. It also shows more clearly that the animals do not regain the lost weight quickly after the drug is removed. As indicated in Figure 2, the body weights of the drug-treated groups appear to still be slowly converging with those of the vehicle control group 7 days after the drug was removed (day 14).

The tolerance of the anorexic effects observed in Experiment 2 did not appear to be due to either the reduced body weight or the state of starvation. Figure 3 below shows that animals whose body weight had been reduced by food deprivation (\boxtimes) to the same degree as that produced by N-0923 (3 mg/kg) (Δ) showed nearly identical additional weight loss when the drug was administered. In addition, allowing the starved animals to free feed did not alter the drug effect, i.e., weight loss from the deprived body weight was similar to that from the undeprived body weight (data not shown).

Experiment 3

Continuous 4-week drug infusion on free-feeding schedule

Thirty-six animals were treated as in Experiment 2 above except that they received minipumps (2ML4) that delivered drugs at 2.5 μ l/hr continuously for 4 weeks. The pumps were loaded with N-0923 (50 μ g/2.5 μ l/hr), amphetamine 7.15 μ g/2.5 μ l/hr) or vehicle (5% dextrose in water). Body weight and food intake measurements were taken for a total of 3 months comprising 1 week prior to pump implantation, 1 month during drug infusion, and 7 weeks after pump removal.

SUBSTITUTE SHEET

-21-

The data summarized in Figure 4 shows that continuous 24-hour infusion of N-0923 at 50 $\mu\text{g}/2.5 \mu\text{l/hr}$ (—) for 4 weeks maintained a lower body weight than the 1-week treatment of the same drug at the same rate (■). These results show that the drug continued to reduce food intake below free-feeding levels and retarded weight gain over the 4-week period in spite of the initial tolerance. After the drug was removed, animals slowly regained body weight over a period of one month until they were equal in weight to vehicle control animals, whose body weight continuously increases due to the effects of captivity.

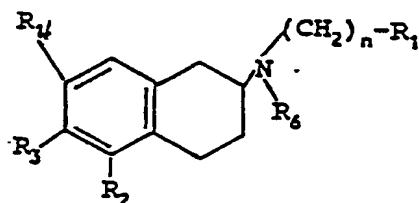
While particular embodiments of the invention have been described, it will be understood, of course, that the invention is not limited thereto since many obvious modifications can be made and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims.

SUBSTITUTE SHEET

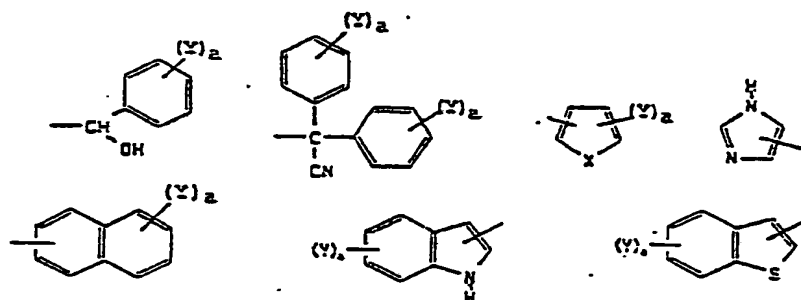
-22-

We claim:

1. A method for inducing anorexia and weight loss in a mammal comprising administering to said mammal an effective amount of a compound selected from the group consisting of the optically active or compounds represented by the formula:



wherein R_1 is selected from the group consisting of methyl, substituted or unsubstituted phenyls, pyridyl, hydroxyphenyl,



X is oxygen or sulfur, Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxy-amido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and hetero atom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorus and said hydrocarbyl radicals comprise from 1 to 12 carbon atoms, and a is an integer of from zero to 3,

SUBSTITUTE SHEET

-23-

R_2 , R_3 and R_4 are each selected from the group consisting of H and OA, A is H or is selected from the group consisting of hydrocarbyl radicals, $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{R}_5$, and $-\overset{\overset{\text{O}}{\parallel}}{\text{CNHR}_5}$,

R_5 is selected from the group consisting of hydrocarbyl radicals; n is an integer between 1 and 3; and R_6 is an alkyl chain having between 1 and 3 carbon atoms with the provision that at least one of R_2 , R_3 and R_4 is H, that at least one of R_2 , R_3 and R_4 is not H, and that R_2 and R_4 are not both OA, and pharmaceutically acceptable salt thereof.

2. The method of claim 1 wherein a is zero and R_2 is OA and A is H.

3. The method of claim 1 wherein the mammal does not undergo a rebound weight gain upon removal from the drug.

4. The method of claim 3 where A is selected from the group consisting of phenyl and alkyl radicals having from 1 to 12 carbon atoms.

5. The method of claim 4 wherein R_5 is selected from the group of alkyl or aryl radicals.

6. The method of claim 5 wherein R_1 is selected from the group consisting of methyl, thienyl, phenyl, indolyl, benzothienyl, hydroxyphenyl, furanyl and naphthalenyl.

7. The method of claim 6 wherein n is 2.

8. The method of claim 7 wherein R_2 , R_3 and R_4 are selected from the group consisting of H and OA wherein A is H, $-\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{R}_5$ and $-\overset{\overset{\text{O}}{\parallel}}{\text{CNHR}_5}$.

SUBSTITUTE SHEET

-24-

9. The method of claim 8 wherein said R_1 is selected from the group consisting of 2-thienyl and 3-thienyl.

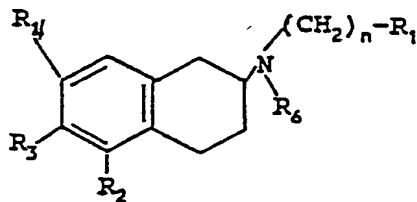
10. The method claim 9 wherein R_4 and R_3 are H and R_2 is OH.

11. The method of claim 10 wherein R_1 is 2-thienyl and said mammal is a human.

12. The method of claim 11 wherein the optically active compound is the (-) isomer.

13. The method of claim 11 wherein the optically active compound is the (+) isomer.

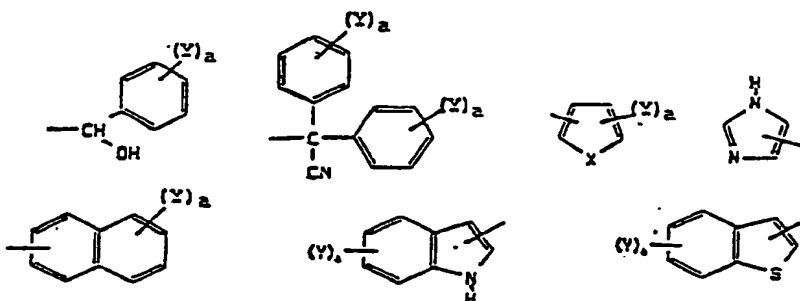
14. The method of activating the D2 dopamine receptors of an obese mammal so as to induce anorexia and weight loss, comprising administering to said mammal an effective amount of a compound selected from the group consisting of optically active compounds represented by the formula:



wherein R_1 is selected from the group consisting of methyl, substituted or unsubstituted phenyls, pyridyl, hydroxyphenyl,

SUBSTITUTE SHEET

-25-



X is oxygen or sulfur, Y is selected from the group consisting of hydroxy, nitro, cyano, azido, amino, acylamino, carboxy-amido, trifluoromethyl, sulfate, sulfonamido, halogen, hydrocarbyl and hetero atom-substituted hydrocarbyl radicals, wherein said heteroatoms are selected from the group consisting of halogen, nitrogen, oxygen, sulfur and phosphorus and said hydrocarbyl radicals comprise from 1 to 12 carbon atoms, and a is an integer of from zero to 3,

R_2 , R_3 and R_4 are each selected from the group consisting of H and OA, A is H or is selected from the group consisting of hydrocarbyl radicals, $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-R_5$, and $-\overset{\text{O}}{\underset{\parallel}{\text{C}}}\text{NHR}_5$,

R_5 is selected from the group consisting of hydrocarbyl radicals; n is an integer between 1 and 3; and R_6 is an alkyl chain having between 1 and 3 carbon atoms with the provision that at least one of R_2 , R_3 and R_4 is H, that at least one of R_2 , R_3 and R_4 is not H, and that R_2 and R_4 are not both OA, and pharmaceutically acceptable salt thereof.

15. The method of claim 14 wherein a is zero and R_2 is OA and A is H.

SUBSTITUTE SHEET

-26-

16. The method of claim 15 where A is selected from the group consisting of phenyl and alkyl radicals having from 1 to 12 carbon atoms.

17. The method of claim 16 wherein R_3 is selected from the group of alkyl or aryl radicals.

18. The method of claim 17 wherein R_1 is selected from the group consisting of methyl, thienyl, phenyl, indolyl, benzothienyl, hydroxyphenyl, furanyl and naphthalenyl.

19. The method of claim 18 wherein n is 2.

20. The method of claim 19 wherein R_2 , R_3 and R_4 are selected from the group consisting of H and OA wherein A is H, $-C-R_5$ and $-CNHR_5$.

$$\begin{array}{cc} \text{O} & \text{O} \\ || & || \\ -C-R_5 & -CNHR_5 \end{array}$$

21. The method of claim 20 wherein said R_1 is selected from the group consisting of 2-thienyl and 3-thienyl.

22. The method claim 21 wherein R_4 and R_3 are H and R_2 is OH.

23. The method of claim 22 wherein R_1 is 2-thienyl and said mammal is a human.

24. The method of claim 23 wherein the optically active compound is the (-) isomer.

25. The method of claim 23 wherein the optically active compound is the (+) isomer.

26. The method of claim 25 wherein the human experiences substantially no side effects to the central nervous system.

SUBSTITUTE SHEET

FIG. 1.

1/2

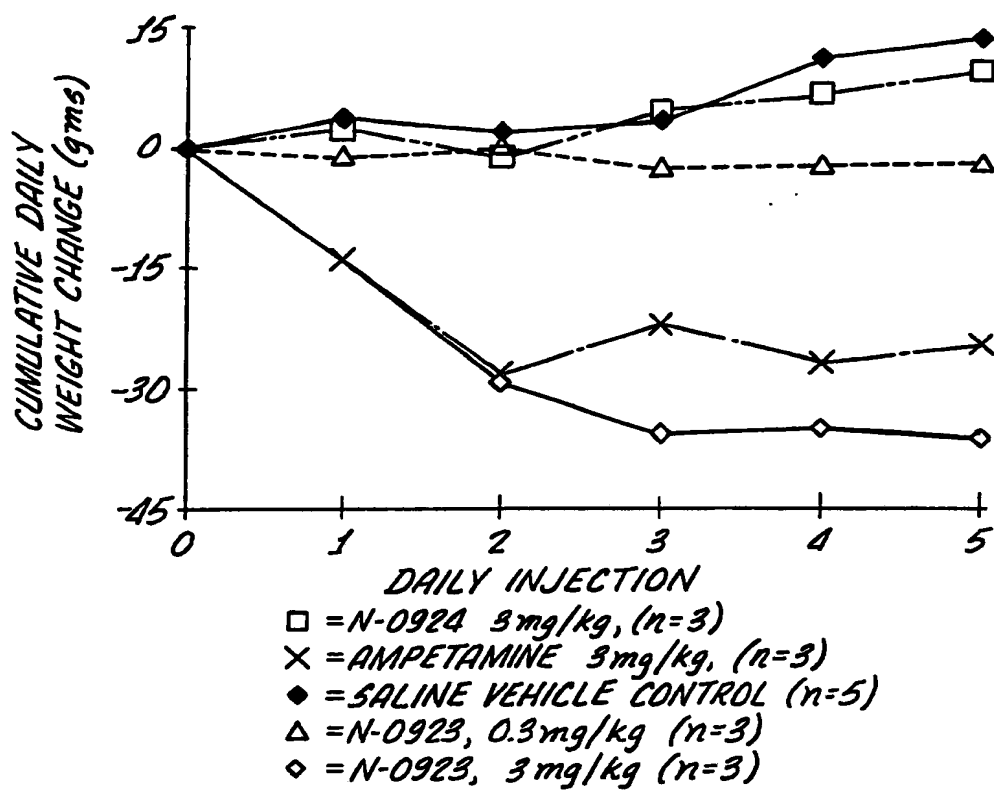
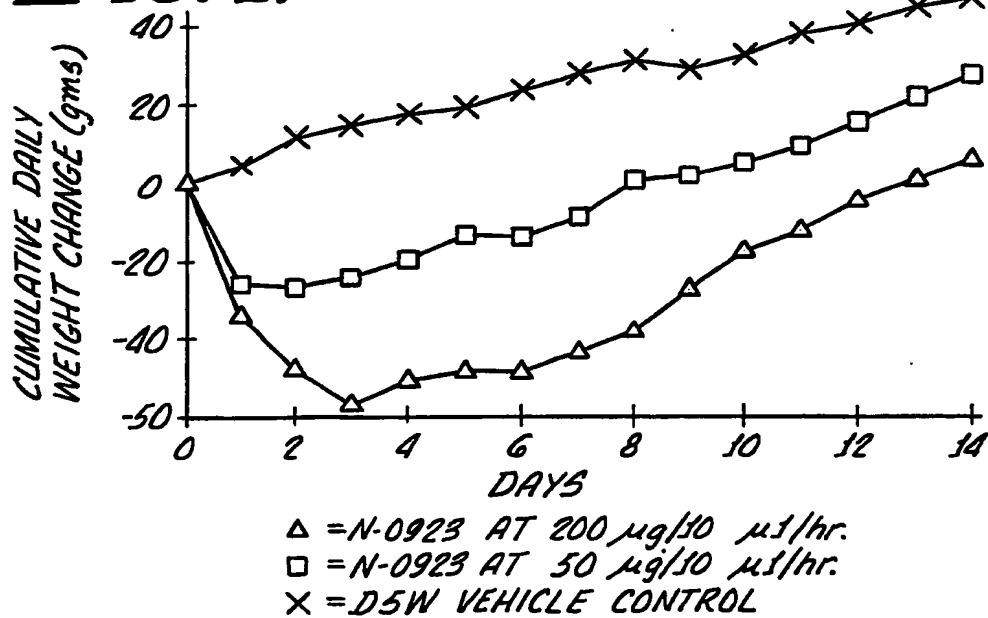
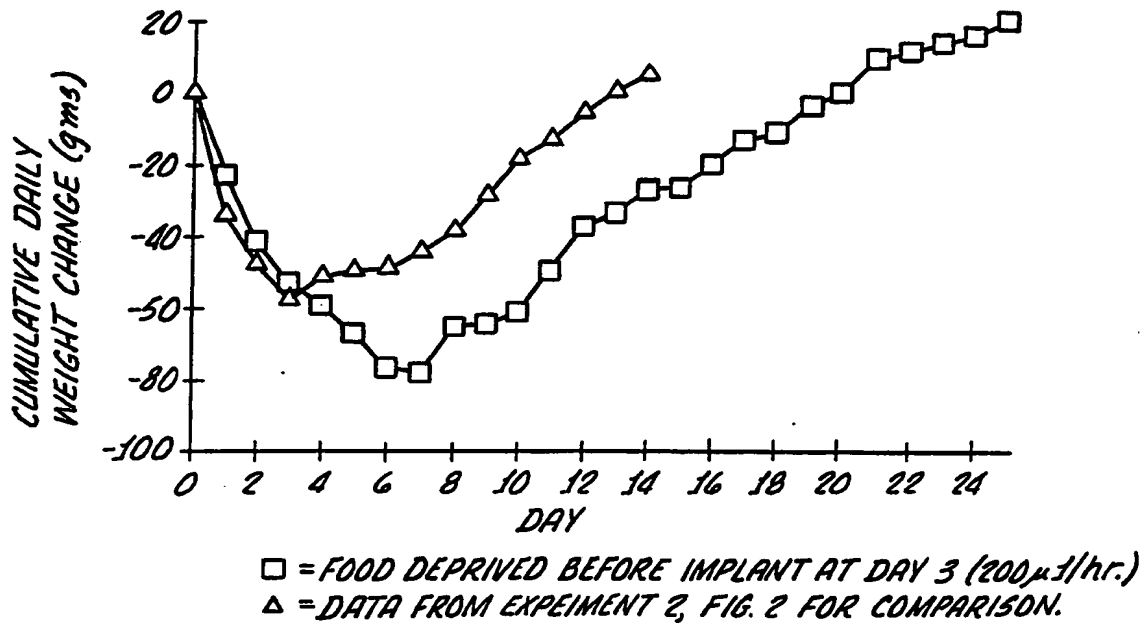
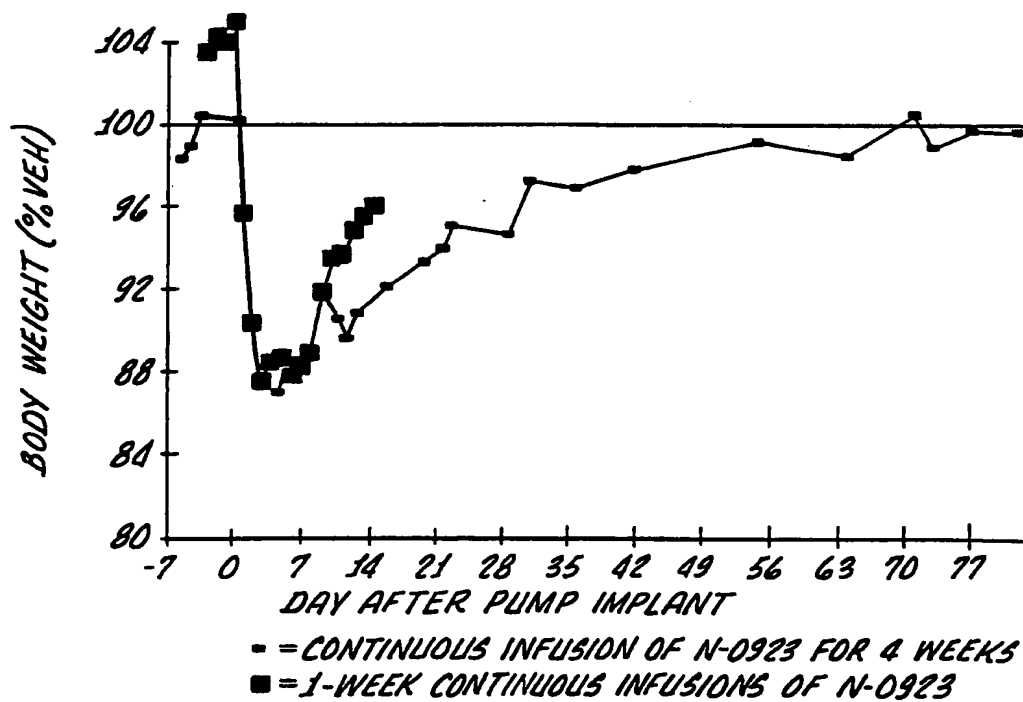
FIG. 2.

FIG. 3.

2/2

**FIG. 4.**

INTERNATIONAL SEARCH REPORT

International Application No PCT/US90/02135

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³ According to International Patent Classification (IPC) or to both National Classification and IPC IPC(5) A61K 31/44, 31/415, 31/405 31/38, 31/385, 31/34 31/275, 31/135 US CL 514/357, 394, 415, 438, 443, 471, 523, 650						
II. FIELDS SEARCHED <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched ⁴</div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 30%; text-align: left; border-bottom: 1px solid black;">Classification System</th> <th style="width: 70%; text-align: left; border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="padding: 5px;">US</td> <td style="padding: 5px;">514/357, 399, 415, 438, 443, 471, 523, 650</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵</div>			Classification System	Classification Symbols	US	514/357, 399, 415, 438, 443, 471, 523, 650
Classification System	Classification Symbols					
US	514/357, 399, 415, 438, 443, 471, 523, 650					
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴						
Category ⁶	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸				
Y	US, A 4,564,628 HORN 14 JANUARY 1986 Entire document	1-26				
Y	US, A 4,189,494 ENGEL, ET AL 19 DECEMBER 1980 Entire document	1-26				
Y	TOWELL, ET AL PSYCHOPHARMACOLOGY (BERLIN) 1986 90(1) 84-71 Chemical Abstract Vol. 105, 1986, Abstract 146158r	1-26				
Y	MCDERMED, ET AL J. Med Chem 1976 19(4) 547-9 Entire document	1-26				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁵ * Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>						
IV. CERTIFICATION						
Date of the Actual Completion of the International Search ¹ <div style="text-align: center; font-weight: bold;">14 MAY 1990</div>	Date of Mailing of this International Search Report ² <div style="text-align: center; font-weight: bold; font-size: 1.2em;">27 AUG 1990</div>					
International Searching Authority ¹ <div style="text-align: center;">ISA/US</div>	Signature of Authorized Officer ²⁰ - <div style="text-align: center;"> EDWARD L. WARD </div>					